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Are Metabolically Healthy Overweight/Obese Men at Increased Risk for Sudden Cardiac Death?

Running head: Metabolically healthy obesity and sudden cardiac death

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Abstract (236 words)

We examined the association between metabolically healthy overweight/obesity and the risk of sudden cardiac death in middle-aged men. This prospective study was based on a population sample of 2185 men aged 42-60 years in the Kuopio Ischemic Heart Disease cohort study. Participants were divided into 4 groups based on body mass index and metabolic health status. Metabolically healthy overweight/obesity was defined as a body mass index ≥25 kg/m^2 without metabolic abnormalities, and metabolically unhealthy normal weight was defined as body mass index <25 kg/m^2 with ≥1 metabolic abnormalities. During a median follow-up of 26 years (interquartile ranges: 18.7-28.1 years), 240 sudden cardiac deaths occurred. Compared with metabolically healthy normal weight men, metabolically unhealthy overweight/obese men had a greater risk of sudden cardiac death (hazard ratio [HR] 1.99, 95% Confidence Interval [CI]: 1.03-3.85) after adjusting for potential confounders. However, metabolically healthy overweight/obese men were not at increased risk of sudden cardiac death (HR 0.95, 95% CI, 0.40-2.24) as compared with their metabolically healthy normal weight counterparts after adjusting for age, smoking, low-density lipoprotein cholesterol, high sensitivity C-reactive protein, insulin, history of myocardial infarction, and directly measured peak oxygen uptake. Our findings indicate that metabolically healthy normal weight men and metabolically healthy overweight/obese men were at comparable risk of sudden cardiac death over a 26 year follow-up period, suggesting that a baseline body mass index ≥25 kg/m^2 per se doesn't adversely impact the risk of sudden cardiac death.

Key words: sudden cardiac death, obesity, metabolically healthy obesity.

Abbreviation

BMI	body mass index
CHD	coronary heart disease
CI	Confidence Interval
CVD	cardiovascular disease
ECG	electrocardiographic
HR	hazard ratio
KIHD	Kuopio Ischaemic Heart Disease Risk Factor Study
MHNW	metabolically healthy normal weight
MHOO	metabolically healthy overweight-obese
MHO	metabolically healthy obese
MUNW	metabolically unhealthy normal weight
MUOO	metabolically unhealthy overweight-obese
SCD	sudden cardiac death

Introduction

Although metabolically healthy obese (MHO) individuals appear to be at higher risk of coronary heart disease (CHD), cerebrovascular disease, and heart failure than their metabolically healthy normal weight counterparts,[1] other studies have reported no association between MHO and cardiovascular events.[2,3] Furthermore, it remains unclear whether differences in body habitus and metabolic health profiles extend to cardiac arrest as a predictable cardiovascular outcome in the general population. Sudden cardiac death (SCD) is a global public health concern, accounting for up to 50% of all cardiovascular deaths. While obesity has been associated with a greater risk of SCD, the impact of overweight/obesity on the incidence of SCD remains unclear due to inherent confounding variables.[4,5] To further clarify these potential risk modulators, we examined the association between metabolically healthy overweight/obese middle-aged men and the risk of SCD over an extended follow-up.

Methods

This prospective investigation included participants in the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD), which is a prospective population-based long-term analysis designed to evaluate risk factors for cardiovascular disease (CVD) and related outcomes in a randomly selected sample of men from eastern Finland. Of the original cohort of 3433 men who resided in the town of Kuopio or its surrounding rural communities, 198 were excluded for varied reasons (eg, serious disease, moved from the area). At baseline, examinations were conducted on 2682 men (82.9% of the eligible population) between March 1984 and December 1989. Participants whose blood markers and anthropometric variables were initially assessed were included in the present analysis (n=2,185, aged 42-60 years). The KIHD study was approved by the Research Ethics Committee of the University of Eastern Finland and all study participants provided written informed consent.

Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Our cohort did not include any participants who were underweight (BMI <18.5 kg/m^2). Resting blood pressure was measured using a sphygmomanometer and was expressed as the mean value from 6 different measurements (3 while supine, 1 while standing, and 2 while sitting). Blood samples were collected in the morning following a 12 hour overnight fast and analyzed according to standard protocols. Laboratory methods and other assessments are described elsewhere.[6] Peak oxygen uptake as an index of cardiorespiratory fitness was directly measured using a computerized metabolic measurement system during an electrically braked progressive cycle ergometer exercise test to volitional fatigue.

Our study population was divided into 4 groups based on cross-classification of BMI and metabolic health status: metabolically healthy normal weight (MHNW); metabolically unhealthy normal weight (MUNW); metabolically healthy overweight-obese (MHOO); and, metabolically unhealthy overweight-obese (MUOO). We used a hybrid MHO definition with a modified BMI (original BMI cut-off was ≥30 kg/m^2) as previously suggested.[7] Being MHOO was defined as a BMI ≥25 kg/m^2 with "0" or no metabolic abnormalities or risk factors as signified by the following: systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mm Hg or antihypertensive drug treatment; high-density lipoprotein cholesterol <40 mg/dL (1.0 mmol/L); serum triglycerides ≥150 mg/dL (1.7 mmol/L) or treatment for hypertriglyceridemia; and fasting blood glucose ≥100 mg/dL (5.6 mmol/L) or treatment with hypoglycemic agents. We excluded waist circumference from the definition of MHO, since most participants met the criteria for a high waist circumference.[7]

SCD was defined as a fatal event that occurred within 1 h after the onset of symptoms or within 24 h when autopsy data did not reveal a non-cardiac cause of SCD or after a fatal

cardiac arrest following successful resuscitation from ventricular tachycardia and/or ventricular fibrillation. Diagnostic classification of events was based on symptoms, electrocardiographic (ECG) findings, cardiac enzyme elevations, autopsy findings (80% of the SCDs) and history of CHD combined with relevant clinical and ECG findings. Data on SCDs were derived from interviews with family members, hospital records, death certificates, autopsy reports and medico-legal documents. A detailed definition of SCD has been previously described.[6]

We calculated the hazard ratio (HR) and 95% confidence intervals (CI) from multivariable Cox proportional hazard model with adjustment for confounding variables to determine the relations of body phenotypes (ie, normal weight, overweight-obese) to the risk of SCD. For the multivariable analysis, potential confounding variables (ie, covariates) were selected as variables with statistically significant differences among groups as shown Table 1. Statistical significance was set at $P<.05$ and analyses were conducted using SPSS version 21.0 (SPSS, Armonk, NY).

Results

Table 1 shows baseline characteristics of the study participants grouped by metabolic health status and body habitus. We found that 193 of the 2,185 participants (8.8%) were classified as MHOO. There were significant differences in age, BMI, smoking, history of myocardial infarction, prevalence of diabetes and hypertension, resting systolic/diastolic blood pressures, lipid/lipoprotein profiles, glucose, insulin, high sensitivity C-reactive protein, and peak oxygen uptake among the 4 groups ($P<.05$).

During a median follow-up of 26 years (interquartile ranges: 18.7-28.1 years), 240 (11%) SCDs occurred. Compared with MHNW men, those who were classified as MHOO were not at increased risk of SCD (hazard ratio [HR] 0.95, 95% Confidence Interval [CI]: 0.40-

2.24) after adjusting for age, smoking, low-density lipoprotein cholesterol, high sensitivity C-reactive protein, insulin, history of myocardial infarction, and peak oxygen uptake. However, MUOO men had a greater risk of SCD (HR 1.99, 95% CI, 1.03-3.85) as compared with their MHNW counterparts (Table 2). The Kaplan-Meier survival analysis showed that the survival rate of SCD in MHOO was similar to that of MHNW cohort (Figure 1).

Discussion

Although obesity is associated with an increased risk of SCD,[3] and selected risk factors may predispose obese men to an increased risk of SCD, it appears that these and other risk factors operate differently in patients with and without preexisting ischemic heart disease.[5] Thus, the impact of obesity on incident SCD remains unclear due to potential confounding variables and/or substantial unexplained variance. Over a 26-year follow-up, we found that men who were MHOO were not at greater risk of SCD as compared with their MHNW counterparts. Our results are consistent with previous reports[2,3,8] and further extend the impact of MHOO on SCD risk as counterintuitively related to 'healthy or unhealthy overweight-obese'.[9]

To our knowledge, this is the first long-term study to report that MHOO men were not at elevated risk for SCD, as compared with their metabolically healthy, normal weight peers. However, additional studies needed to confirm these results. In contrast, the largest prospective study to date, over a 5.4 year follow-up, found that MHO persons were at increased risk of CHD, cerebrovascular disease, and heart failure, but not peripheral vascular disease, as compared with MHNW individuals.[1] Interestingly, a sub-group analysis with a relatively long-term follow-up (>10 years) reported that subjects with MHO were at increased risk of all-cause mortality and CVD events.[2] Another investigation using the strictest definition for metabolic

health, that is, no metabolic abnormalities, found no association between MHO and CVD events.[3] However, the analysis had limited statistical power.

We believe that varied definitions of metabolic health, body habitus (eg, obesity vs overweight-obesity), follow-up durations and gender differences may, at least in part, be responsible for the conflicting data in the literature. Furthermore, another reason for these conflicting results may be the inability to account for physical activity/cardiorespiratory fitness as important potential confounding variables.[9-11] It is interesting to note that those studies that adjusted for cardiorespiratory fitness or physical activity did not find increased risk of CVD mortality in MHO,[12,13] which is compatible with the present findings. In our 26 year follow-up study, after adjusting for potential confounders, including cardiorespiratory fitness, MHOO men were not an increased risk of SCD as compared with MHNW men.

In reference to the association between body habitus, cardiometabolic risk factors and the risk of SCD, our results showed that MUNW men were not at a significantly greater risk for incident SCD than their MHNW counterparts. However, the risk for incident SCD in MUNW men appears to be at greater than that of MHNW men. The present findings are consistent with previous studies that reported increased risk of mortality in MUNW as compared with MHNW.[14] Accordingly, strategies of prevention/treatment should consider the individual's metabolic health status as an important confounding variable in overweight/obese individuals and in normal weight individuals. However, additional studies are needed to further clarify the relation between metabolically unhealthy non-obese individuals and the risk of SCD.

We acknowledge several methodologic limitations. Because our study population included only men, we were unable to determine whether this association extends to women. Although we adjusted for numerous potential confounders, other variables that we did not

assess may have influenced these associations. Unfortunately, our database did not include selected ECG variables, specifically QRS duration, QT intervals, and the Tpeak-Tend interval, as well as heart rate variability and left ventricular ejection fraction, all of which may be related to the incidence of SCD. Inclusion of these parameters in future studies would provide additional mechanistic insights relative to the associated risk modulators. In addition, our total SCDs (n=240) and study cohorts were relatively small, especially MHNW (n=232) and MHOO (n=193), and we grouped overweight and obese men together into the MHOO subset. It remains unclear whether similar results would have been obtained using only obese individuals (BMI $\geq$30 kg/m^2) to characterize the MHO phenotype,[15] rather than combining overweight and obese participants into one cohort. Finally, we categorized our 4 study groups based on BMI and cardiometabolic risk factors only at baseline, and acknowledge that body habitus and/or metabolic profiles may have changed over time. Despite these limitations, strengths of this study include the assessment of outcomes over a long-term follow-up (a median of 26 years; interquartile ranges: 18.7-28.1 years), and that cardiorespiratory fitness, a strong potential confounder which is often either estimated or unaccounted for in major MHO related studies,[10,11] was directly measured as peak oxygen uptake.

Conclusion

Our results demonstrate that compared with MHNW men, MUOO men had greater risk of SCD, but MHOO men were not at increased risk of SCD after adjusting for potential confounders, including cardiorespiratory fitness, over a 26 year follow-up.

Conflict of Interest

The authors have no disclosures regarding potential conflicts of interest relative to this manuscript.

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Figure Legends.

Figure 1. Kaplan-Meier survival curves for sudden cardiac death among the metabolically healthy and unhealthy normal weight and overweight-obese men. Log-rank test (Mantel-Cox) for survival difference between the various curves (MHNW vs. MUNW, *P*=.039; MHNW vs. MHOO, *P*=.601; MHNW vs. MUOO, *P*<.001; MUNW vs. MHOO, *P*=.165; MUNW vs. MUOO, *P*=.020; MHOO vs. MUOO, *P*=.002).

Table 1. Baseline characteristics of the participants according to metabolic health status and body habitus (n=2185).

Variables	MHNW (n=232)	MUNW (n=439)	MHOO (n=193)	MUOO (n=1321)	*P*-value
Age (years)	52.3±5.8	52.4±5.0	52.5±5.1	53.2±4.9	.003
Body mass index (kg/m^2)	23.0±1.4	23.4±1.3	27.2±2.2	28.7±2.9	<.001
Smokers (%)	40.5	38.3	36.3	26.6	<.001
Family history of coronary heart disease (%)	46.6	52.2	46.6	50.3	.687
History of myocardial infarction (%)	6.5	5.0	7.8	8.3	.050
Diabetes (%)	0.0	3.4	0.0	8.1	<.001
Hypertension (%)	0.0	24.6	0.0	25.7	<.001
Systolic blood pressure (mmHg)	117.1±7.4	135.0±14.5	117.5±7.6	139.5±16.4	<.001
Diastolic blood pressure (mmHg)	76.7±4.9	89.0±8.6	77.9±4.8	92.8±9.8	<.001
High-density lipoprotein cholesterol (mmol/L)	1.47±0.3	1.34±0.3	1.34±0.2	1.23±0.3	<.001
Low-density lipoprotein cholesterol (mmol/L)	3.86±0.9	4.01±1.0	4.02±1.0	4.06±1.0	.031
Triglycerides (mmol/L)	0.86±0.3	1.14±0.7	0.99±0.3	1.45±0.9	<.001

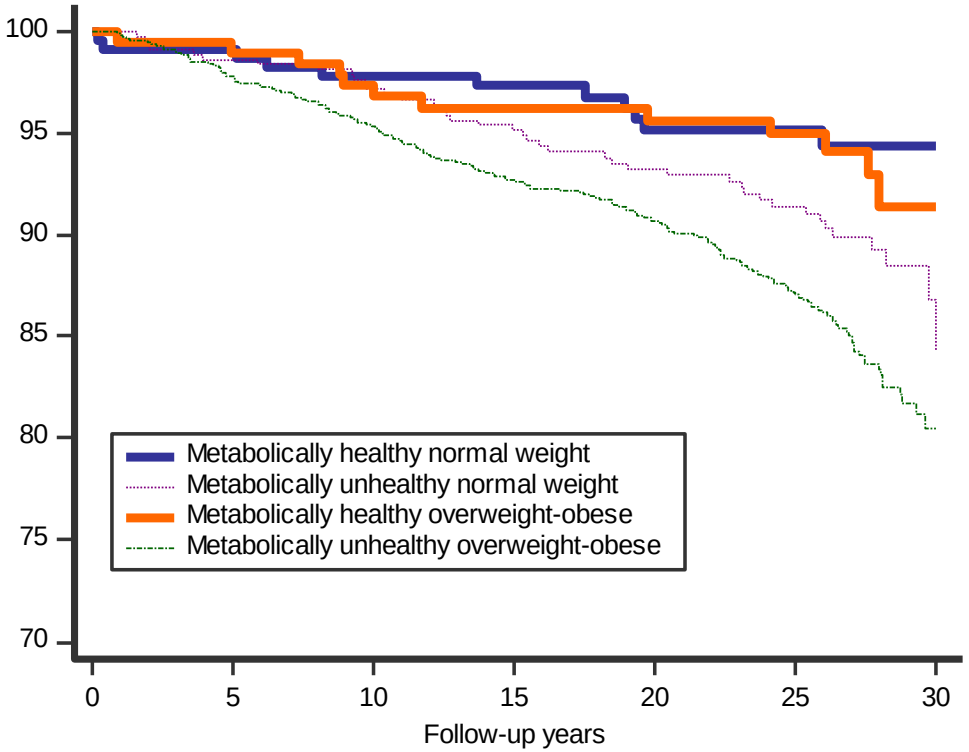
Glucose (mmol/L)	4.41±0.4	4.56±0.7	4.49±0.4	4.93±1.3	<.001
Insulin (mU/l)	7.42±2.8	8.71±3.2	10.37±5.6	13.53±8.0	.001
C-reactive protein (mg/L)	1.81±4.6	1.90±3.0	2.25±3.9	2.54±3.3	.001
Peak oxygen uptake (ml/kg/min)	34.8±8.9	32.9±8.0	31.4±7.2	28.3±7.3	<.001

Data are mean (standard deviations) or percentage. MHNW: metabolically healthy normal weight; MUNW: metabolically unhealthy normal weight; MHOO: metabolically healthy overweight-obese; MUOO: metabolically unhealthy overweight-obese

Table 2. Multivariate hazard ratios (95% CI) of sudden cardiac death across metabolic health status and body habitus.

Variables	Multivariate Hazard ratios (95% CI)
Sudden cardiac death	
Metabolically healthy normal weight	1 (ref)
Metabolically unhealthy normal weight	1.91 (0.95-3.82)
Metabolically healthy overweight-obese	0.95 (0.40-2.24)
Metabolically unhealthy overweight-obese	1.99 (1.03-3.85)

Adjusted for age, smoking, low-density lipoprotein cholesterol, high sensitivity C-reactive protein, insulin, history of myocardial infarction, and peak oxygen uptake.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